Environmental Health
PERSPECTIVES
Journal of the National Institute of Environmental Health Sciences

ehponline.org

# FETAL CHLORPYRIFOS EXPOSURE: ADVERSE EFFECTS ON BRAIN CELL DEVELOPMENT AND CHOLINERGIC BIOMARKERS EMERGE POSTNATALLY AND CONTINUE INTO ADOLESCENCE AND ADULTHOOD

**Dan Qiao, Frederic J. Seidler, Charlotte A. Tate, Mandy M. Cousins and Theodore A Slotkin**

**doi:10.1289/ehp.5828 (available at http://dx.doi.org/)**
**Online 30 October 2002**

The National Institute of Environmental Health Sciences
National Institutes of Health

**EHP 5828 (revised)**

# FETAL CHLORPYRIFOS EXPOSURE: ADVERSE EFFECTS ON BRAIN CELL DEVELOPMENT AND CHOLINERGIC BIOMARKERS EMERGE POSTNATALLY AND CONTINUE INTO ADOLESCENCE AND ADULTHOOD[1]

Dan Qiao, Frederic J. Seidler, Charlotte A. Tate,
Mandy M. Cousins and Theodore A Slotkin

Dept. of Pharmacology & Cancer Biology
Duke University Medical Center
Durham, NC 27710

Running title: Developmental neurotoxicity of chlorpyrifos

Key words: Brain development
Chlorpyrifos
Choline acetyltransferase
Cholinesterase
Development
DNA
Hemicholinium-3 binding
Muscarinic $m_2$-acetylcholine receptor

Abbreviations: ANOVA, analysis of variance
ChAT, choline acetyltransferase
CPF, chlorpyrifos
HC-3, hemicholinium-3
$m_2$AChR, $m_2$-muscarinic acetylcholine receptor

Correspondence: Dr. T.A. Slotkin
Box 3813 DUMC
Room C162, LSRC Building
Research Drive
Dept. of Pharmacology & Cancer Biology
Duke University Medical Center
Durham, NC 27710 USA
Tel (919) 681-8015
Fax (919) 684-8197
E-mail: t.slotkin@duke.edu

[1]Supported by USPHS ES10387 and ES10356.

## ABSTRACT

Fetal and childhood exposures to widely-used organophosphate pesticides, especially chlorpyrifos (CPF), have raised concerns about developmental neurotoxicity. Previously, biomarkers for brain cell number, cell packing density and cell size indicated that neonatal rats were more sensitive to CPF than were fetal rats, yet animals exposed prenatally still developed behavioral deficits in adolescence and adulthood. In the current study, we administered CPF to pregnant rats on gestational days 17-20, using regimens devoid of overt fetal toxicity. We then examined subsequent development of acetylcholine systems in forebrain regions involved in cognitive function, and compared the effects to those on general biomarkers of cell development. Choline acetyltransferase, a constitutive marker for cholinergic nerve terminals, showed only minor CPF-induced changes during the period of rapid synaptogenesis. In contrast, hemicholinium-3 binding to the presynaptic choline transporter, which is responsive to nerve impulse activity, displayed marked suppression in the animals exposed to CPF; despite a return to nearly-normal values by weaning, deficits were again apparent in adolescence and adulthood. There was no compensatory upregulation of cholinergic receptors, as $m_2$-muscarinic cholinergic receptor binding was unchanged. CPF also elicited delayed-onset alterations in biomarkers for general aspects of cell integrity, with reductions in cell packing density, increases in relative cell size and contraction of neuritic extensions; however, neither the magnitude nor timing of these changes were predictive of the cholinergic defects. The current findings indicate a wide window of vulnerability of cholinergic systems to CPF, extending from prenatal through postnatal periods, occurring independently of adverse effects on general cellular neurotoxicity.